RISK ASSESSMENT-
TRANSPORTATION OF MEDICINAL PRODUCTS

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August 2018

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Tekijä/Författare – Author Elina Viitanen		
Työn nimi / Arbetets titel – Title Risk Assessment- Transportation of medicinal products		
Oppiaine /Läroämne – Subject Industrial Pharmacy		
Työn laji/Arbetets art – Level Industrial Pharmacy Thesis	Aika/Datum – Month and year August 2018	Sivumäärä/ Sidoantal – Number of pages 37

It is the responsibility of the marketing authorization holder to assure that the safety and integrity of the medicinal products is not jeopardized during any phase of the manufacturing process, including transportation. In the last resort it is the marketing authorization holder´s decision how the transportation of medicinal products is controlled and safe and good quality products provided to the patiens. Transportation of medicinal products in European Union area is regulated by EU Good distribution Practise (GDP) guidelines.

There are different characteristics for different modes of transportation. While the air freight is most often the fastest mode of transportation, it is also most vulnerable for temperature excursions during loading and unloading the aircraft. The road transportation can in best case provide swift door to door delivery, in worst case the road transportation can be time consuming with many different intermediate storaging locations and many loading phases. Road transportation is also the riskiest mode of transportation in matter of crime. In general, the cargo is in danger whenever the vehicle is not moving. While sea freight is the slowest mode of transportation, in some cases it can be suitable for use. With sea freight big amounts of cargo can be transported simultaneously and rather safely even very long distances. Both air and sea freight require additional mode of transportation from and to airport and port. This is called multimodal transportation.

Ultimately the decision of the mode of transportation is a compromise with pros and cons from the different modes of transportation. Some of the risks related to transportation process can be mitigated with the proper risk management. One risk management tool is risk assessment. In case of transportation, risk assessment provides a wide look of the whole transportation chain.

Avainsanat – Nyckelord – Keyword
Risk assessment, GDP, mode of transportation, safety

Säilytyspaikka – Förvaringställe – Where deposited
Faculty of Pharmacy

Muita tietoja – Övriga uppgifter – Additional information
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Tiedekunta/Osasto Fakultet/Sektion – Faculty Farmasian Tiedekunta	Osasto/Sektion– Department -	
Tekijä/Författare – Author Elina Viitanen		
Työn nimi / Arbetets titel – Title Risk Assessment- Transportation of medicinal products		
Oppiaine /Läroämne – Subject Teollisuusfarmasia		
Työn laji/Arbetets art – Level Teollisuusfarmasian tutkielma	Aika/Datum – Month and year Elokuu 2018	Sivumäärä/ Sidoantal – Number of pages 37

Tiivistelmä/Referat – Abstract

Myyntiluvan haltijan vastuu on varmistaa, ettei lääkevalmisteiden turvallisuus tai koskemattomuus vaarannu missään valmistusketjun vaiheessa, mukaanlukien lääkevalmisteiden kuljetuksen aikana.

Viimekädessä myyntiluvan haltija on vastuussa siitä miten lääkevalmisteiden kuljetusta kontrolloidaan, jotta potilaille voidaan tarjota turvallisia ja laadukkaita lääkevalmisteita. Euroopan Unionin alueella lääkkeiden kuljetuksen viranomaisvaatimukset on säädetty lääkkeiden hyvät jakelutavat (GDP) -ohjeistossa.

Eri kuljetusmuodoilla on kaikilla omanlaisensa ominaispiirteet. Siinä missä lentorahti on usein nopein kuljetusmuoto, se on erittäin altis lämpötilan vaihteluille lentokoneen lastaus- ja purkuvaiheissa. Maantiekuljetus voi parhaassa tapauksessa olla nopea ovelta- ovelle kuljetus, mutta pahimmassa tapauksessa kuljetukseen kuluu aikaa ja se voi sisältää useita kuorman lastauksia ja purkuja eri välivarastoihin. Maantikuljetus on myös kuljetusmuodoista kaikkein riskialttein rikoksille. Yleisesti voidaan sanoa, että maantiekuljetuksen lasti on vaarassa silloin kun ajoneuvo ei liiku. Vaikka merirahti on hitain kuljetusmuoto, joissain tapauksissa se voi olla tarkoitukseen parhaiten sopiva Hitaudesta huolitatta, meriteitse saadaan kuljetettua samanaikaisesti suuria tavaramääriä suhteellisen turvallisesti pitkiäkin välimatkoja. Sekä meri- että lentorahdit vaativat toisenlaisen kuljeutusmuodon käyttöä satamasta tai lentokentältä kohteeseen. Täytä kutsutaan monimuoto-kuljetukseksi.

Lopulta päätös kuljetusmuodosta on kompromissi eri kuljetusmuotojen hyvien ja huonojen puolien välillä. Joitakin kuljetukseen liittyviä riskejä voidaan pienentää kunnollisella riskien hallinnalla. Yksi riskien hallinnan työkalu on riskiarvio. Kuljetusten riskiarvio antaa kattavan kuvan koko kuljetusketjusta.

Avainsanat – Nyckelord – Keywords
Riskiarvio, GDP, kuljetusmuoto, turvallisuus

Säilytyspaikka – Förvaringställe – Where deposited
Farmasian tiedekunta

Muita tietoja – Övriga uppgifter – Additional information
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1 INTRODUCTION

Global supply chains of pharmaceutical products are in many cases very complex. Numerous of variable events are possible during the transportation of medicinal products. The risk managements processes of the pharmaceutical company has the key role in assuring the safety and quality of the products. Even though the authority quidelines set the minimum requirements for assuring the safety and the quality of the medicinal products, it should be the company´s top priority anyway.

Eversince the European Comission published the Good Distribution Practice guideline in 2013, the transportation of medicinal products have gained more attention in the industry. Since 2013 11 wholesalers have lost their wholesale license due to non compliance with the current EU GDP (Eudra GMDP).

The aim of this project was to conduct a risk assessment of transportation of medicinal products for company´s use. Along with the risk assessment project, a literature review of the variables affecting transportation was compiled.

2 LITERATURE REVIEW

The transportation chains of medicinal products are complex, including multiple different outsourced activities in transportation companies, multiple different transportation routes, variance in modes of transportation and changes in seasonal weather conditions in different parts of the world (EU Good Manufacturing Practice, Annex 15, 2015). This complexity exposes the global supply chains for theft (van Diest et al., 2017). Theft of pharmaceutical cargo endangers the safety and integrity of the products, but it may also jeopardize the patient safety by causing stock-out situations in the market. Vast majority of the counterfeit or falcified medicinal products originate from the legal supply chain (European Comission, 2011). Medicinal products can be stolen during legal supply chain, modified or falcified by the criminals and re-entered to legal supply chain with falcified documentation and unauthorized wholesaler (Italian Medicine Agency, 2015). Despite the complexity of the supply chain, transportation of medicinal products should be arranged so that quality and integrity of the product is not compromised (EU Good Distribution Practice, Chapter 9, 2013).

2.1 Transportation of medicinal products - Authority requirements

There are many regulations for transportation of pharmaceutical products depending on the manufacturing country and / or distribution territory (“Good Distribution Practice “ European Medicine Agency Reference: 14.4.2018). Just to name few, transportation of pharmaceutical products is regulated by EMA (European Comission Good Distribution Practice, 2013), World Health Organization (WHO Annex 5, Good Distribution Practice for pharmaceutical products, 2010) and United States Pharmacopeia (USP Good storage and Distribution practices for drug products, 2018). The regulations set minimum standards for transportation of medicinal products (“Good Distribution Practice “ European Medicine Agency Reference: 14.4.2018). The content of the three regulations is the same, transportation of the medicinal products should be

arranged in a such way that is does not compromise the quality or the safety of the product (European Comission, 2013; WHO 2010; USP). All three regulations also require that modes of transportation, transportation routes and the equipment used in the transportation should be suitable for use. The different variables during the mode of transportation should also be evaluated carefully, when making decisions of the modes of transportation or transportation route for each product. Unlike EU GDP, both USP and WHO Annex 5 require risk evaluation in the case of using dry ice on the transportation of medicinal products. Currently only WHO Annex 5 requires drivers to identify themselves before loading the vehicles. Continuous monitoring of the transportation conditions is required unless justified, as per EU GDP by risk assessment of the transportation route, or as per USP by stability data of the product.

European Medicine Agency Good Distribution Practice set the minimum requirements for transportation of pharmaceutical products in Europe (“Good Distribution Practice “ European Medicine Agency Reference: 14.4.2018). EU GDP requirements for transportation are presented in Table 1.

Table 1: EU GDP requirements for transportation of medicinal products (EU GDP, 2013)

General requirements	"Risk based approach should be utilized when planning transportation"
	"Delivery route risk assessment to be conducted, for determining the need of temperature control"
	"Deliveries can be made only to address stated in the delivery note"
Vehicles	"Vehicles must be suitable for use or procedure should be to ensure that quality of the product is not compromised."
	"Written maintenance plan should be available for vehicle and equipment"
	"Equipment for temperature control should be maintained and calibrated at least once a year"
Temperature:	"Labelled storage conditions should be maintained during transportation"
	"Process should be available for investigation and handling of temperature excursions"

In addition to GDP chapter 9 (Transportation) requirements, there are also other chapters that most often have effect on transportation such as Quality System, and Outsourced activities (EU GDP, 2013). For pharmaceutical product manufacturers in EU, the mandatory guideline to follow is the EU Good Manufacturing Practice (EU GMP 2010).

2.2 Authority requirements – non compliance

Since 2013, two pharmaceutical wholesalers have lost their wholesale license due to lack of compliance in transportation related issues (Eudra GMDP, noncompliance Reference 14.4.2018). Transportation related issues are also causing many major deficiencies in GDP inspections (Brown et al., 2017). In 2016, transportation related issues were the second biggest group with 13% of all major deficiencies given by MHRA GDP inspectors. When looked more closely into transportation related deficiencies, transportation itself is the biggest cause for deficiencies, while significantly lower amount of deficiencies were related to products requiring special conditions. Justifications for major deficienciens are presented in Table 2.

Table 2 Major deficiencies on transportation related topics in MHRA GDP inspections in 2016 (Brown et al., 2017)

Deficiensy
"There was inadequate reassurance that a robust process was in place assessing the need of temperature controls for ambient storage medicinal products across the full range of the company's transport arrangements, including third party distribution services"
"The site utilized uncontrolled ambient transportation for customer delivery with no risk assessment or definition of responsibilities with customers"
"Uncalibrated equipment was being utilized to monitor the temperature during transportation."
"Risk assessment identifying the need for temperature controls for the company´s own transportation arrangements lacked detail and contained erroneous assumptions concerning UK climatic conditions."
"It could not be demonstrated that ambient medicinal products had been shipped in a manner to ensure temperature conditions are maintained within acceptable limits during the entire journey."

2.3 Risk assessment(s) of transportation

As required by EU GMP Annex 15, risk assessment of transportation must be done (EU GMP Annex 15, 2015). However, the annex states, risk evaluation should not be limited to risks, which are continuously under control or are being monitored, but the risk evaluation should be extended to other risks as well. The number of risks related to transportation is limitless, for example; customs related issues, theft, product or packaging related risks, duration of the transportation, temperature control, value of the goods, vibration during the transportation, patient safety related risks etc. (Spiggelkötter, 2014).

Risk assessment process contains three parts: risk identification, risk analysis and risk evaluation (International Council for Harmonization (ICH) Q9, 2006). The process starts with risk identification. There are different tools available to assist in the risk identification process, for example brainstorming, what if –

analysis, mind mapping, fish bone diagram or whatever helps to identify the risks related to topic (Jenkins et al., 2010).

Once risks have been identified the risk management tools are used for analyzing and evaluating the effects of the risks (ICH Q9, 2006). Useful tools for risk analysis are for example Fault Tree Analysis (FTA), Hazard Analysis and Critical Control Points (HACCP) or Failure Modes Effect Analysis (FMEA) (Jenkins et al., 2010). FTA is a useful tool but requires thorough process understanding. Because FTA analysis gives a visual map of different failures, it is a good tool to increase process understanding. However, it can be time consuming even though focus is quite narrow. The fault tree analysis is designed for identifying the root cause(s) of the unwanted event (Alverbro et al. 2010). The results of the FTA analysis can be qualitative or quantitative. Example of the fault tree analysis diagram (Figure 1.).

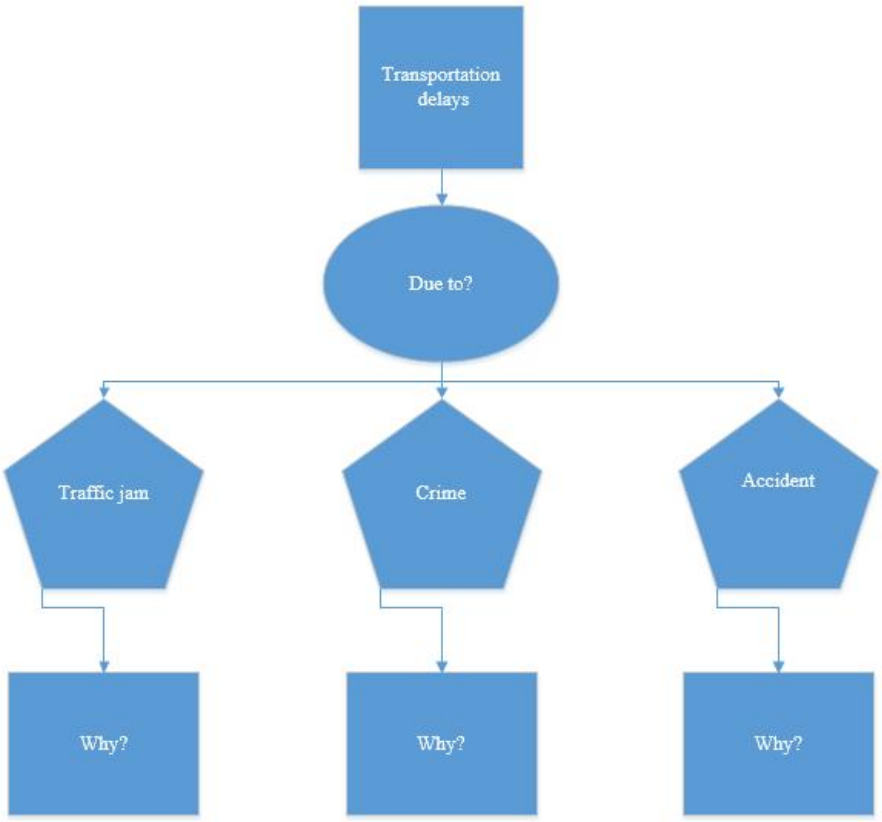

Figure 1. Fault tree analysis

HACCP is a combination tool with risk assessment and risk control features (Jenkins et al., 2010). HACCP starts with drawing detailed process flow, hazard (causing harm to product) identification and analyze if reduction or elimination of the risk is needed. Critical points of the process are then identified and target limits for critical levels set. Process performance at the critical points should be monitored and corrective and preventive actions put into operation. HACCP is a good tool for increasing process understanding, but it can be too heavy for other purposes. FMEA is easy tool and as output of the analysis gives a clear indication of the risk severity as Risk Priority Number (RPN). FMEA is often used to prevent unwanted events from happening (Alverbro et al., 2010). In the FMEA, each risk evaluated by its severity, occurrence and detectability (Jenkins et al., 2010). Final RPN scoring is result of multiplying severity, occurrence and detectability. In the risk analysis phase, the identified risks are given a qualitative description for example low, medium or high risk. Risk evaluation process decided based on previous identification and analysis phases, whether the risk is accepted as such or it should be reduced. Most often it is recommended to use more than one method for example FTA and FMEA (Alverbro et al., 2010).

Before Action										After Action(s) taken			
Risk	Failure Mode	Effect of Failure	Severity	Potential causes	Occurrence	Current controls	Detection	Risk Score	Recommended action	Severity	Occurrence	Detection	Risk score

Figure 2. Failure mode and effects analysis (FMEA table) (Jenkins et al., 2010)

2.3.1 Outsourcing

Majority of the transportation activities of pharmaceutical products is outsourced (Bishara et al., 2014). For outsourced activity, there must be a written quality agreement between the parties (GDP, 2013). Quality agreement can be more than just a list of requirements (Bishara et al., 2014). With the help of written agreement, the roles, responsibilities, requirements, expectations and working methods are always available and known for both parties. A quality agreement should be the basis of the partnership and if properly used, it should also make the partnership stronger.

Good co-operation requires mutual understanding of requirements of both parties (Bishara et al., 2014). Together with the stakeholders, identification of the critical process steps and ongoing risk mitigation is essential. Clear and regular communication between stakeholders, mutually agreed Key Performance Indicator (KPI) targets and performance monitoring, deviation management, root cause and corrective and preventive actions (CAPA) follow ups are listed as key points in good partnership in the pharmaceutical product transportation chain.

2.3.2 Air freight

Though transportation via air freight might be the fastest mode of transportation, it is a multiphase and complex process (Majic et al., 2016). Air freight process starts from the shipper's warehouse, followed by delivery to airport by freight forwarder, storing the cargo at the terminal, flight to destination airport, storing at the destination airport and finally freight forwarder delivery to consignee warehouse (Transco International, Process of Airfreight, 2016). Many different stakeholders are involved in the handling of the goods at the airport: including handling agents, airport warehouse operators and carriers (Majic et al., 2016). Risks related to air freight are listed in Table 3. The most critical steps in air freight are the loading and unloading phases, during which there is a significant risk of temperature excursions and exposure to outside weather conditions. The

temperature excursions or exposure for weather conditions might also happened during the delivery from the terminal to the vessel, because aircraft might also be parked far away from the carriers inbound cargo terminal. Regardless of the fast transportation time, the goods might be spending relatively long time waiting in the terminal to be shipped. Long storing times at the terminal makes the storing time also a critical process step.

Table 3: Risk related to air freight (Majic et al., 2016).

Process step	**Location**	**Risks**	**Effect of the risk**
Shipment preparation	Manufacturer	Packaging process quality Shipment documentation	Damage Delay
Loading /Unloading	Manufacturer /transportation company /airport operators	Duration of the loading and tarmac exposure times Environmental conditions Damages Availability of the shielded decks Training of the personnel Loading sequence (last out of the controlled storage, can be the last one loaded to vehicle)	Temperature excursion Damage of the goods Delays
Transportation (road)	Transportation vehicle	Training of the driver Set point(s) of the container Availability of proper vehicle and containers	Cross contamination Temperature excursions
Storage	Airport	Proper storage conditions Proper storage area Training of the personnel	Temperature excursions
Flight	Air Craft	Availability of the temperature controlled cargo compartments	Temperature excursions

Due to many risks related to air freight, airlines have lost significant profits to safer modes of transportation (Majic et al., 2016). In 2014 International Air Transport Association (IATA) launched a qualification program; Center of Excellence for Independent Validators (CEIV). Qualification program is assigned for parties involved with air transportation chain including for example

airlines, ground handling companies, freight forwarders, road transportation companies, distributors and airports. The aim of the qualification program is to offer better compliance towards pharmaceutical industry's special requirements. When pharmaceutical companies are selecting partners for air freight, the CEIV certified companies should be favored.

2.3.3 Ground freight

Like in air transportation, the biggest risks of road transportation are also related to loading and unloading phases (van Asselt et al, 2015). Other risks related the transportation via road were: way of loading, which may cause product damage or issues with temperature control, temperature control during driver´s breaks, ferry tips or fuel loss. There are also separate risks related to mode of the truck (mono- or bitemperature trailer). Use of bitemperature trailers requires attention during the container set point settings and cargo loading order in order to maintain two different temperature zones in one truck container. Also separate risks related to full truck load (FTL) or less than full truck load (LTL) were identified. Comparison of the risks related to FTL and LTL are listed in Table 4.

Table 4: Comparison of the risks- full truck load vs. less than full truck load (van Asselt et al, 2015).

Operation	**Full truck load**	**Less than truck load**
Number of pickups	One	Multiple
Delivery to recipient	Direct	Via hub/warehouse
Other cargo	No other cargo	Co-loading from other shippers
Lead time	Short	Long
Number of contractors /subcontractors	Limited	Multiple
Risk of temperature excursions	Low	High

Thermotrucks (truck with the reefer/cooling unit) used in transportation of the pharmaceutical products, should be accompanied with alarm systems (van Asselt et al, 2015). The alarm system will send message to the driver in case the temperature changes outside the set point range or in case the equipment stops

working. Better planning of the transportation, might enable the companies to book bi-temperature trailers and also book full truck loads. With full truck load transportation, there is a smaller risk for temperature excursion due to loading phases, smaller risk for cross contamination from other cargo. In addition, the transportation with full truck load is quicker.

By inspecting the vehicles and containers in advance, many risks can be avoided (van Asselt et al, 2015). The pre-loading inspection should at least include checking that the temperature set point(s) are correct, the trailer is visually clean and free from odor, equipment is working properly and the locks are in place. The planning of transportation route and pre-check of the suitable appliances should be done carefully in order to mitigate risk along the route. For transportation in special conditions, for example, the driver should be prepared for minor repairs during the transportation if it is known that the condition of roads is poor. Or in case the transportation is during winter or in extreme weather conditions, pre-check-list should include a check of vehicle materials suitability for extreme temperatures.

Only after the pre-loading inspection is done, the cargo should be loaded into the trailer (van Asselt et al, 2015). The loading of trailers, must be planned carefully in order to avoid unnecessary movement of the cargo and allowing free air flow inside the trailer. In order for the air to flow freely, the pallets must be free from wrapping from all four sides and pallets cannot be loaded too close to doors. During transportation the temperature control system should be checked regularly and the driver should walk around the vehicle after each break, to ensure that there is no breaking into to trailer and that the alarm and temperature ranges have been set correctly.

2.3.4. Sea freight

Transportation via sea can be considered the safest mode of transportation (Edwards, 2017). Risks related the maritime transportation are mostly related to

safety of the ships (Soares et al., 2001). In case of accidents in the maritime transportation, the costs of human life, environmental impact, loss of goods and lost profits are bigger than related to other modes of transportation. The loading of the sea shipment is done at the consignors' warehouse (Edwards, 2017). The container is then sealed until arrival to consignee warehouse. There is a big difference in the quality of the reefer containers available in different areas. Poor quality of a reefer container increases the risk of cross contamination and temperature excursion. It is recommended that the reefer containers should not be more than 5 year old and shipping lines should provide a pre-trip inspection form for justifying the conditions of the reefer container. The use of thermal blankets or passive packing solutions can reduce the risk of temperature changes during the times the reefer container is out of power. The reefer containers and its equipment should be a maintained according to manufacturer maintenance. Also in order to reduce the commercial risks in case of accidents, insurance of the marine cargo should be in place.

Planning of the sea freight is important (Edwards, 2017). Due to multiple stakeholders involved in the sea freight, many issues must be discussed well in advance the actual transportation. It should be agreed when the suitable reefer containers will be available, pre- tip inspection forms of the containers should be reviewed and it should be agreed with the transportation company and the port operators that the container must be transferred into areas with electricity as soon as possible once container is delivered to port. Risk effects and mitigation suggestions are presented on Table 5.

Table 5: Risk effects and mitigation suggestion for risks related to sea freight (Edwards 2017)

Risk	**Risk effect**	**Mitigation**
Container quality	Cross contamination, temperature excursions	Accept max 5 year old reefer containers
Availability of goods quality reefer container	Delay	Quality agreements, supplier management
Long delivery time	Delay	-
Reefer container power	Temperature excursion	Co-operation with the stakeholders

2.3.5. Multimodal transportation

Mode of transportation with more than one mode of transportation is called multimodal transportation (Majic et al., 2016). Example of multimodal transportation is for example, air freight where the goods are first delivered to airport with truck, and then cargo is unloaded to terminal storage area, later loaded into air craft and then back to truck for delivery to customer. Multimodal transportation is often used in global supply chains (Vilko and Hallikas 2010). As the multimodal transportation is a combination of different modes of transportation, also risks related to multimodal transportation are more od less the same as the risks related to each mode of transportation separately. Risks related to multimodal maritime transportation and supply to mainland Finland are listed in Table 6. Overall the five biggest risks related to multimodal transportation in Gulf of Finland were employee strikes in port, fire, ice conditions and slipperiness in wintertime and information systems. Lack of trust

and co-operation between the different stakeholders was named as one of the biggest challenges in multimodal transportation and its risk management.

Table 6 Most common risks related to multimodal transportation at Gulf of Finland (Vilko and Hallikas 2010).

Risk category	Risk (two biggest)
Supply risk	Bottle necks on transportation route, employee strike on port
Operational risk	Conditions on cargo handling equipment, motivation of the workforce
Security risk	Information systems, organized crime
Macro risk	Financial crisis, competition in transportation sector
Policy risk	Russian customs
Environmental risk	fire and ice conditions during wintertime.

2.3.6. Theft

Amount of counterfeit or falsified pharmaceutical products is increasing ("Falcified Medicinenes" European Medicine Agency: (Reference 14.4.2018)). Falsified medicinal products reach patients via legal and illegal supply chains (EU Falsified medicinal directive, 2011). There are big regional differences in the amounts of falsified or counterfeit products on the market (Abril et al., 2016). In the developing countries over 30 % of the pharmaceutical market can be counterfeit or falsified. In the developed countries the amount is approximately 1%. Counterfeit or substandard medicinal products can be products that have initially failed the quality requirements (El- Jardali et al 2015). Majority of the illegal drug products are stolen (Riccardi et al., 2014).

Due to increased security in the pharmaceutical facilities, the majority of the thefts of pharmaceutical products occur during transportation (van Diest et al, 2017). The risk of theft of pharmaceutical products in Europe is relatively low

(Ekwall et al., 2015). Out of all the recorded cargo theft cases in Europe, Middle East, and Africa, the theft of pharmaceutical products is only 1%. Risk level of cargo theft is highly dependent on the route of transportation and risk level varies highly in different parts of Europe. Even though the risk of theft towards pharmaceutical products is still overall quite small, the risk in Italy is significantly higher. In Italy, 9% of all recorded cargo theft cases include pharmaceutical products. That makes Italy a high risk area for pharmaceutical product transportation. High number of theft cases for pharmaceutical products, especially in Southern and Eastern parts of Italy is explained by influence of Italian Mafia and other criminalized groups on the transportation companies (Riccardi et al., 2014). Figure 3 indicates the most risky areas in relation to all kinds of cargo theft in Europe.

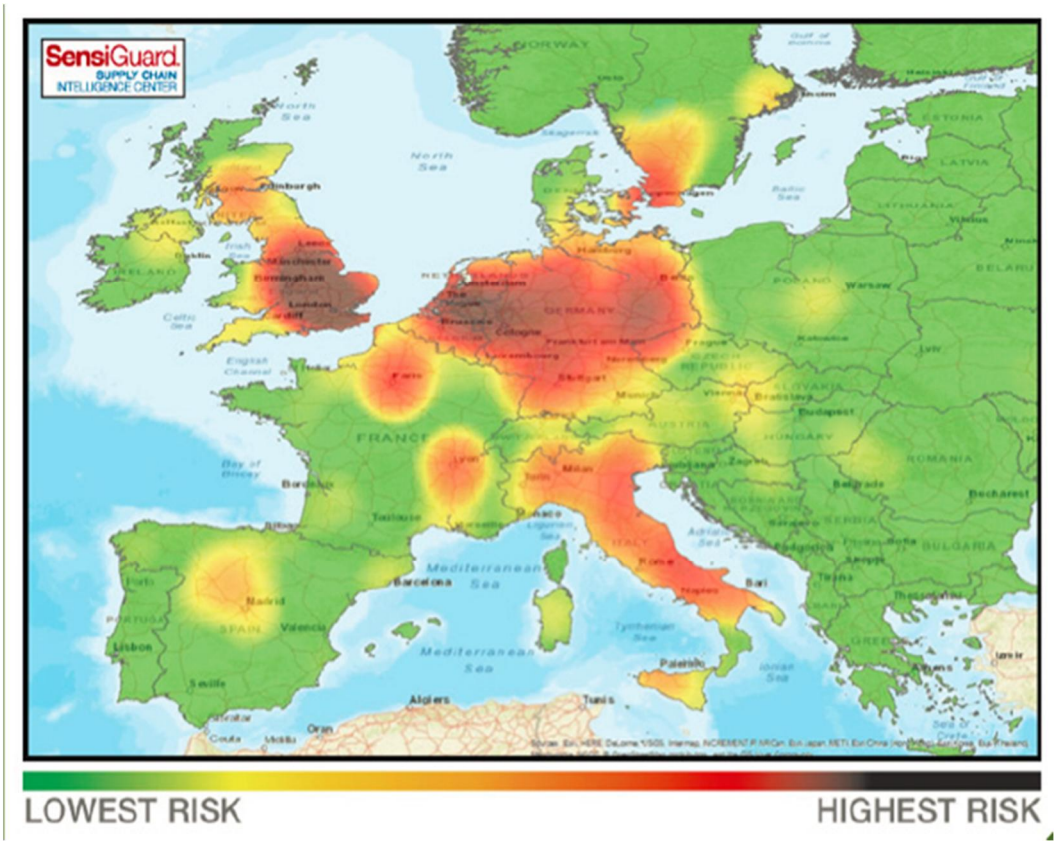

Figure 3. Cargo theft risk map (Van Diest et al., 2017)

Total 61% of all cargo thefts happen while the vehicle is not moving i.e. vehicle is parked at truck parks or at the service stations (International Road Transport Union (IRU), 2018). The risk of theft from a trailer at unsecured parking lot is significantly bigger than the risk related to secured parking (Ekwall et al., 2015). Transportation via road is the most vulnerable for theft (van Diest et al., 2017).

The security of the sea freight is better than of airfreight, because the shipment container doors are sealed until arrival at consignee warehouse (Edwards, 2017). In case the seal has been opened during the shipment, it will be noticed latest at the consignee warehouse. The number of pirate attacks has been decreasing since 2010 (Statista, 2018). The regions with risk of piracy attacks are Indonesia, Philippines, Somalia and Nigeria.

The driver has the key role in preventing the crime during transit (van Diest et al., 2017). The driver should be aware of the high risk areas, know how to behave in case of incidents and should be given regular security trainings. By keeping few basic things in mind when planning the transportation route, the security risks can be reduced by avoiding passing through the high risk areas, having the breaks at secured parking areas, minimizing the times when the vehicle is left unattended, preferring using dual drivers, avoiding unnecessary stops and avoiding driver habits (having break always at the same place etc.). In order to mitigate the risk of stolen cargo, drivers should identify themselves as well as show the necessary papers in order to assure that they are authorized for the transportation (WHO Annex 5, 2010).

There are also security monitoring solutions, CCTV´s or GPS tracking devices available (van Diest, at al., 2017). The programs monitor the cargo on-line and immediately report in case of tampering the trailer. GPS tracking and device can be also combined with temperature monitoring device (“Conventional Temperature Monitors” Sensitech, Reference 26.4.2018).

2.3.7 Weather conditions- temperature, humidity

The product stability can be jeopardized during transportation by exposing the product to environmental conditions such as heat, light and moisture (Kommanaboyina and Rhodes, 1999). Even though medicinal products should be transported within their labelled storage conditions, the loading and unloading phases might expose the goods to outside temperature and weather conditions (van Asselt et all, 2017). Also closing and opening the vehicle doors, malfunction of the reefer equipment as well as leaks in the transportation container may expose the product on environmental conditions during transit.

Packaging materials for each pharmaceutical product should be selected and tested according to guidelines (WHO Annex 9, 2002). The packaging materials should protect the product from outside conditions (temperature, light and moisture) that might endanger the products stability. In addition to primary and secondary packing materials the risk of moisture, light and temperature can be reduced by for example using active or passive packing systems or other packing solutions (Rosskoss 2011). For products requiring close monitoring of the temperature conditions, active or passive solutions should be used. Table 7 illustrates the differences between active and passive packing solutions.

Table 7: Active and passive packing solutions (Rosskoss 2011).

Active	**Passive**
Needs external power	External power not needed
Simple to pack	Consignment preparation under controlled environment
Temperature controlled handling during transportation required	Temperature specific handling during transportation is not needed
Costs are the same for bigger and smaller volumes	Flexible for different volumes
Multi use	Mono use
High costs	Less costly

For products which are not temperature sensitive, lighter solutions such as thermal blankets can be used (Basta 2017). The basic idea of the thermal blanket is to reflect sunlight and provide some extra insulation for the product. Thermal

blankets are available for different levels of insulation; from slight degree of insulation to very high degree of insulation against physical and thermal changes. When selecting the suitable protection for the products few things should be kept in mind (BioPharm International Editors, 2013). Bigger surface area absorbs more thermal radiation which means, by increasing the insulation layer, the dimensions of the pallet are growing and surface area grows. White color and glossy materials should be favored because it reflects heat radiation better than dark and matte surface. Metalized covers are bigger risks for temperature excursion due to materials conductive nature. For example polyethylene covers could be used instead. The protection against temperature excursion can be effectively extended by increasing the thermal energy inside the package. Thermal energy can be increased by using for example gel bags inside the thermal cover. This way the changes in temperatures inside the packaging will be significantly slower. For example when 20º C 5ml vial was placed in a room of 30º C it took 8 minutes for the vial liquid to reach 25º C, while the same took 10 hours from the same vial to reach 25º C when surrounded with room temperature gel bag.

A useful tool for evaluations of temperature excursions is the use of Mean Kinetic Temperature (MKT) (ICH Q1A R2). MKT is a single calculated temperature at which the total amount of degradation over a particular time point is equal to the sum of the individual degradations that would occur at various temperatures (USP Good Storage and Shipping Practice). Temperature excursion can be evaluated with the help of MKT- temperature; however the evaluation of minimum and maximum temperatures is important, too. In case temperature excursions are out of available stability data, MKT value should not be used as justification. MKT is higher than the calculated mean temperature, because the higher temperature values are given greater weight (Equation 1).

$$T_K = \frac{\frac{-\Delta H}{R}}{ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)}, \quad (1)$$

where ΔH is the heat of activation, which equals 83.144 kJ per mol (default value; unless more accurate information is available from experimental studies), R is universal gas constant, which equals 8.3144 x 10-3 kJ per degree per mol, T1 is the (average) temperature, in degrees Kelvin, during the first time point, T2 is the (average) temperature, in degrees Kelvin, during the second time point, Tn is the (average) temperature, in degrees Kelvin, during the nth measured time point; n being the amount of the measured time points and T_K is the result in degrees Kelvin. The final result MKT (in degree Celsius) will be calculated by doing simple subtraction (TK – 273.15°K)

In addition to transportation vehicles equipment, temperature and humidity conditions can be measured for example with the help of dataloggers (“Conventional Temperature Monitors”, Sensitech. Reference 26.4.2018). Many datalogger models can calculate the MKT value automatically.

3 RISK ASSESSMENT PROJECT

The aim of the project was to conduct a risk assessment for transportation on a general level to fulfill EU GDP and GMP Annex 15 Qualification and validation requirements. The project started by determining the scope. The selected scope for the risk assessment includes both inbound and outbound logistics. Inbound logistics include deliveries of raw materials (API ´s and excipients) and external supply products (bulk and finished product). Outbound logistics include deliveries to partners and wholesales. Out of risk assessments scope are the external supply deliveries, where product's Marketing Authorization Holder (MAH) is a partner, sample shipments, outbound logistics where partner is responsible for the transportation, internal transportation between different plants of the company and courier shipments.

A group of six experts from different areas of expertise were nominated for the project. Risk assessment project was divided into three workshops. First workshop was to identify the risks, second to analyze risks and third to evaluate the risks. As supporting data for risk analysis, company's transportation deviation data from 2016 to 2018 was categorized and evaluated.

3.1 Risk identification

Risks were identified with help of fish bone diagram (Ishikawa diagram, Figure 4). All risks mentioned in the risk identification workshop were written down. In total of 101 risks were identified.

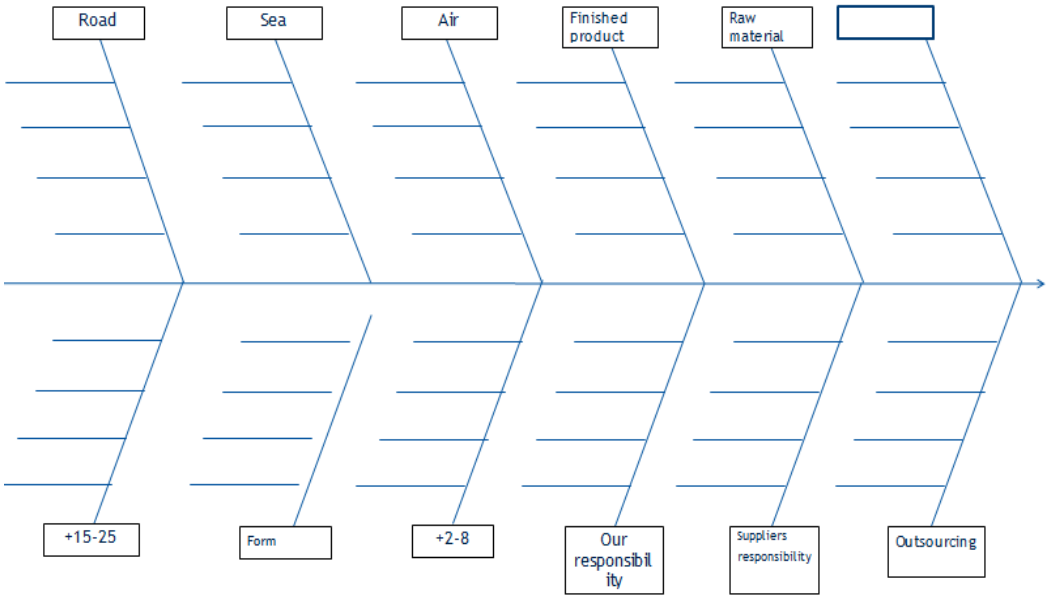

Figure 4: Fishbone diagram

3.2 Risk analysis

The identified risks were categorized into three different main categories: General risks, inbound risks and outbound risks. Each main category was then divided into subcategories. Categorization of the risks is clarified in Table 8. In risk analysis, the effects of each risk was further described and current controls were listed. Current controls were listed based on the company´s relevant SOP´s, quality agreements and the knowledge of the expert team.

Table 8: Categorization of the risks

Risk analysis (categorization of the risks)		
General risks		
	Subcontracting	
	Accidents	
	Commercial issues	
Inbound risks		
	Raw materials	
	External Supply	
		Road
		Air
		Sea
Outbound risks		
	Road	
	Air	
	Sea	

3.3 Risk evaluation

Risks were analyzed with Failure Mode and Effect Analysis (FMEA) by the expert team. For each risk, points were given for its severity, occurrence and detectability. Risk scoring is presented in Table 9. In case the scoring was not based on the facts or supporting data, scoring was based on the opinion of the expert team. Company´s transportation deviation data from 2016 to 2018 was the basis for occurrence scoring.

Table 9: Scoring of risk severity, occurense and detectability.

Severity	
	1= Low risk (no effect on the quality of the product)
	2 = Medium risk (may have an effect on the quality of the product)
	3 = High risk (clear effect on the quality of the product)
Occurrence	
	1= Rare (less than once a year)
	2= Medium (1-5 times a year)
	3= Often (more than 5 times a year)
Detectability	
	1= always detected or n/a
	2= Difficult to detect
	3= impossible to detect

Risk point number (RPN) was calculated for each risk by multiplying points of severity, occurrence and detectability. As a result each risk was categorized as low risk (RPN 1-4), medium risk (5-8) or high risk (9-27). Results of the risk assessment were presented to Quality Management and Supply Chain management. Risk mitigation actions were started for risks with high classification. Residual risks were accepted for the other category risks.

3.4 Results and discussion

The risks were categorized into three category; general, inbound and outbound logistics. Outsourcing came up with the highest risk points in the general risk category. Outsourcing was named as high risk operation due to its complexicity

and difficulty to control. Even though the roles and responbilities must be clearly described and controlled in the quality agreements, outsourcing can still be challenging to control (Bishara et al., 2014). Company currently controls outsourcing in many ways, such as instuctions for goods receive process, standard operating procedures as well as clear and inclusive agreements with the wholesalers, partners and subcontractors. With the current controls many of the risks related to outsourcing can be detected at the company´s warehouse (inbound logistics) and at the wholesaler warehouse (outbound logistics). For example, temperature excursions during transportation will be detected once dataloggers are downloaded at the receiving warehouse, damabed packages will be detected at the goods receive inspection. The company also arranges regular meetings with the key suppliers and partners.

Out of all modes of transportation, air freight was detected as the most riskiest (Majic et al., 2016). Even though total number of identified risks related to air freight is lower than with road transportation, more high level risk were identified in air freight. Majority of the risks of air freight were related to temperature control, divided deliveries or mixups. Due to complexicity of the air freight chain, it was identified as extremely challenging to control.

Both sea and air freight are strictly controlled, thus less risky for crime, unlike road transportation. The number of security related risks were highest on road transportation. Road transportation is the only mode of transportation in which only the driver is responsible for the safety of the cargo (van Diest et al., 2017). Road transportation is also vulnerable for other risks such as mixups during loading and unloading phases and other external risks (for example addition of prohibited materials into shipping container etc.). The review of company´s deviation data from 2016-2018 also reflects the safety issues of the road transportation. Deviations were recoded during two years review period where the truck had been broken in or prohibited products delivered in the same containers space with the medicinal products. No such deviations were recorded neither for air freight, nor sea freight.

Sea freight was detected as the least risky mode of transportation (Edwards, 2017). Sea shipment containers are sealed at the consignors warehouse and seals cannot be opened during the transportation. Due to that fact, shipment container are well protected against crime or temperature deviations. However, in case of any defect during the sea freight, the amount and value of cargo affected is usually bigger than with other modes of transportation.

There were no major differences between inbound and outbound risks. The difference between inbound and outbound logistics is the company´s role. On the inbound logistics the company works as the receiving site and on the outbound logicstics the company´s role is the consignee. The risks related to each mode of transportation were the same regardless of the inbound or outbound logistics standpoint.

Total amount of identified risks per each category are presented in Table 10. Risks are categorized as per the risk classification as well as total number of risks.

Table 10: Risk assessment results (number of risks identified)

INBOUND (number of risks)				
	LOW	**MEDIUM**	**HIGH**	**Total**
General	2	0	1	3
Raw materials	10	1	1	12
Road	14	9	1	24
Air	13	0	5	18
Sea	14	1	0	15
OUTBOUND (number of risks)				
	LOW	**MEDIUM**	**HIGH**	**TOTAL**
General	2	0	2	4
Road	18	7	1	26
Air	12	2	4	18
Sea	15	0	0	15

The risk assessment project results are in line with the literature review. Overall in the risk assessment project, quite many identified risks were already controlled by the company´s current risk mamagement process. In such cases, eventhough the severity of such risk was given high points, most often the detectability was then given low points, because, with current controls, the defects are always or very often noticed with company´s standard process.

3.5. Conclusions

Complex transportation chains, multiple modes of transportation and changes in the outside weather conditions make the control challenging. Both risk assessment results as well as literature review conclude that overall the air freight is the most riskiest mode of transportation. Especially, the tarmac phase

of the air freight causes temperature deviations and lack of control at the airport causes divided deliveries.

The outcome of the risk assessment project as well as the literature review is in line with copany´s current experience of the risks related to transportation of medicinal products. The results of the risk analysis also confirm that the company´s current controls are effective in preventing and detecting the possible deviations in the transportation. The risk assessment project also revealed the areas which required further improvements, i.e. recidual risks. Detailed plan for recidual risk mitigation was also issued and presented to the management team.

Currently there is a lack of independent studies regarding transportation of medicinal products. However, because risk assessment of transportation is a GMP requirement, the pharmaceutical companies might have issued the studies internally.

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